

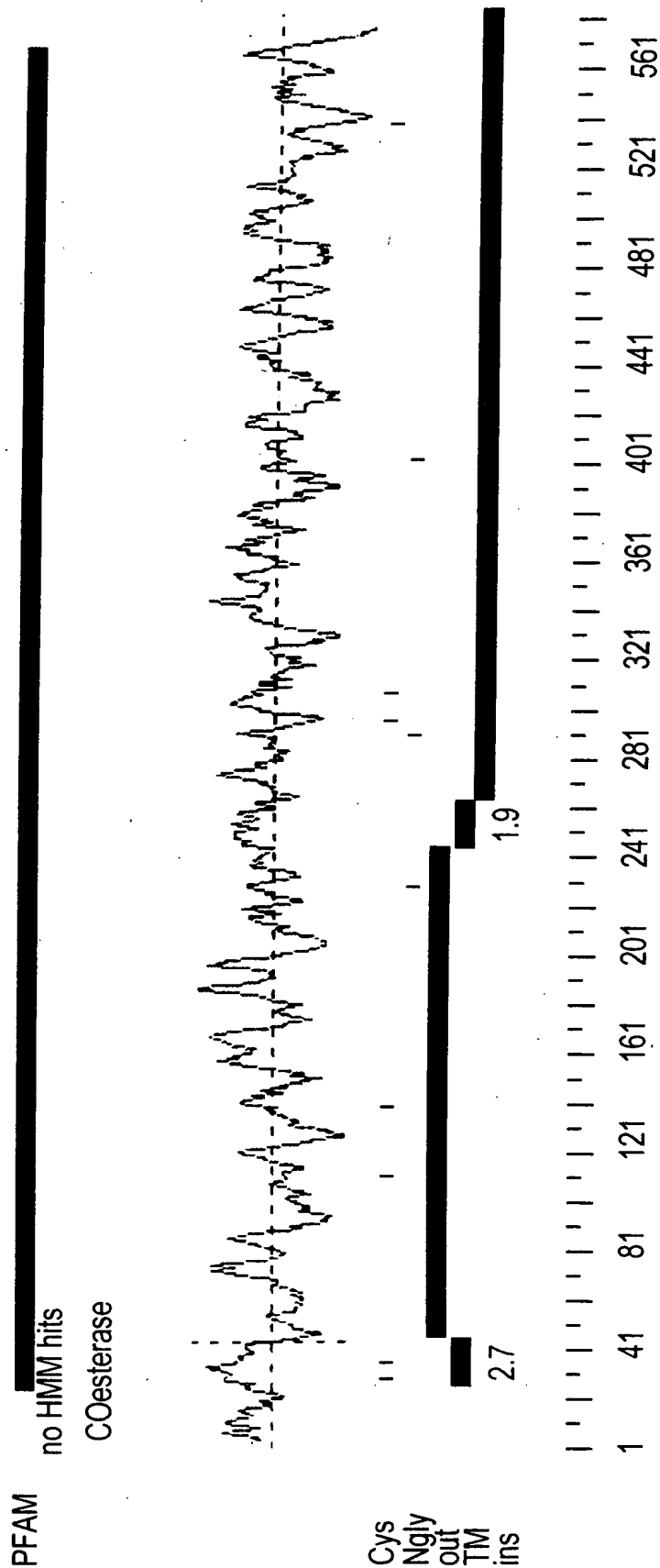


REPLACEMENT SHEET

Applicant: Rosana Kapeller-Libermann, et al.  
Title: METHODS OF USING 18903 TO TREAT PAIN AND PAIN-RELATED DISORDERS  
Application No.: 10/001,227  
Attorney/Agent: Mario Cloutier  
Docket No.: MPI00-408PIRM

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FIG. 1





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## FIG. 2A

Protein Family / Domain Matches, HMMer version 2

Searching for complete domains in PFAM

hmmpfam - search a single seq against HMM database

HMMER 2.1.1 (Dec 1998)

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HMMER is freely distributed under the GNU General Public License (GPL).

HMM file:

/prod/ddm/seqanal/pfam/pfam6.4/pfam

Sequence file:

/prod/ddm/wspace/orfanal/oa-script.6214.seq

Query: Fbh18903FL

Scores for sequence family classification (score includes all domains):

Model	Description	Score	E-value	N
COesterase	Carboxylesterase	558.6	4.1e-164	1

Parsed for domains:

Model	Domain	seq-f	seq-t	hmm-f	hmm-t	score	E-value
COesterase	1/1	25	569	1	612	558.6	4.1e-164

Alignments of top-scoring domains:

COesterase: domain 1 of 1, from 25 to 569: score 558.6, E = 4.1e-164

\*-&gt;mvl1llfll1lllliaavlalaaakaspdl1VatnnVlcGkvrGvnek

+1+ +L 1 1 ++ +l+a+++ ++ V t++ G++ G++

18903 25 RWILCWSLTLC1MAQTALGALHT---KRPQVVTKY---GTLQCKQM 65

tdngeqsvysFlGIPYAepFVGnLRFkaPqPykepWsdvldAtkyppsCl

+ ++ +FlG+P+ PP+G LRF +P+P +epW+++dat+ypp Cl

18903 66 VGKT--PIQVFLGVFSPPLGLILRFAPPEP-PEPWKIGIRDATTYPGCL 112



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FIG. 2B

QdddfgfsldLKvalkmlslgwnklvg...lklSEDCLYLNvytpknt  
Q + +g+ 1+++ ++ + + 1 +SEDCLYLNvy P+ +  
18903 113 Q-ESWQ-----LASMYVSTREYkWLRFSEDCLYLNvyAPARA 150

kpnsklPvmVwIhGGGFmgGshslplslYdgeslaregnVivVsiNYRL  
+ + +lPvmVw +GG+F +G++ s+Y g+ la++++V++V ++ RL  
18903 151 PGDPQLPVMVWFFGGAfIVGAA-----SSYEGSDLAAREKVVLVFLQHRL 195

GplGLstgddklpgsGNyGLlDQrlAlkKWqdNIaaFGGDPnsVTifGe  
G++GFLst+d+++ GN+GLlDQ +Al+WVq+NIAaFGGDP++VT+fG+  
18903 196 GIFGFLSTDDSHAR--GNWGLlDQMAALRWVQENIAAFGGDPGNVTLFGQ 243

SAGaaSVsl1lllSngGDNppsskgLFhRAIsqSGsalspwaigsesnarg  
SAGa+S+s l++s p++ gLFhRAIsqSG+al +i+s+ +  
18903 244 SAGAMSISGLIMS-----PLA-SGLFhRAIsqSGTALFRlFITSNP--LK 285

rakelarllGCnetsssellCLRsksaeeLleatrsfllfeyvpflplf  
ak++a l+GCn++s l+ CLR s + + + + + f + +f +  
18903 286 VAKKVAHLACNHNSTQILVNCRLALSGTKVMRVSNK-MRFLQlNFQRDP 334

1....aFgPvvdGdDapeafipedPeelikeGkfadvPyliGvtdEGgy  
++ + +PvvdG+ +ip+dP+ l+ +Gk + vPyl Gv++ E+ +  
18903 335 EeiwSMSpVVDGV-----VIPDDPLVLLTQGVSSVPYLLGVNNLEFNW 379

faaml1nasskgedelkktetnpdvwllellkyllyfayasealnikmdldlad  
+++++++ + + ket++ l+ 1l+ + +  
18903 380 LLPYIMKFPLNR-QAMRKETITK-MLWSTRTLLN-ITKEQ-----VP 418

kvlekYpgdvddfsvesrkpnlgdmltdllFkcptrvaadlhakhggsPv  
v e+Y++ v + + ++ + d++ D +F+++ + ++ ++++g Pv  
18903 419 LVVEEYLDNVNEHDWKLNRNMDIVQDATFYA-TLQTAHYHRDAGLPV 467



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FIG. 2C

18903 468 YLYEFEHHAR-----GIIVKPRTDGADHGDEMYFLFGGPFATG-LS-- 507  
YaYvfdhpsfgigQflakrvdpefggavHgdEiffvFgnpllleqlyka  
Y+Y+f h+a+ + v+p+++ga+HgdE++f+Fg p+ ++ 1  
teeeeeksstkmmnywanFAktGnPnngtsnglvWpkytseeqkyslli  
e++ts +mm+ywanFA+tGnP n++ +l+ Wp y+++e +l+  
18903 508 MGKEKALS-LQMMKYWANFARTGNP-NDG--NLPCWPRYNKDEK--YLQL 551  
llttitaqklkardprkvlcnfw<-\*  
+tt +klk+++ ++fw  
18903 552 DFTTRVGMKLEKK-----MAFW 569

//

Searching for complete domains in SMART



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## FIG. 3A

GAP of: FrGcgManager\_76\_IOA81nWg\_ check: 5132 from: 1 to: 1983

Fbh18903FL - Import - vector trimmed

to: FrGcgManager\_76\_JOA3WXZ1\_ check: 1319 from: 1 to: 2456

z34105 in Patent Nucleotide

Symbol comparison table: /ddm\_local/gcg/gcg\_9.1/  
1/gcgcore/data/rundata/nwsgapdna.cmp  
CompCheck: 8760

Gap Weight:	12	Average Match:	10.000
Length Weight:	4	Average Mismatch:	0.000
Quality:	13796	Length:	2746
Ratio:	6.957	Gaps:	14
Percent Similarity:	92.617	Percent Identity:	92.617

Match display thresholds for the alignment(s):

| = IDENTITY  
: = 5  
. = 1

FrGcgManager\_76\_IOA81nWg\_ x FrGcgManager\_76\_JOA3WXZ1

..

```
COE-2      1 .....CCT 3
Z34105 101 CATTTCGCCTTGCTGACGGCGTCGAGCCCTGGCCAGACATGTCCACAGGG 150
          4 TTAGCCAATTCGGCCGAGGCCTCCCGCCCCAGTA.CTTGCTGGCAGGGAT 52
          || || | ||| | ||| ||| ||| ||| ||| ||| |||
151 TTCTCCTTCGGGTCCGGGACTCTGGGCTCCACCACCGTGGCCGCCGGCGG 200
          53 TAAGAGCAGA.TAAAAGTGTGCTCACACACTGTAGACACGGCTACCATGC 101
          | |||| | ||| ||| | ||| ||| ||| ||| |||
201 GACCAGCACAGGCGGCGTTTTCTCCTTCGGAACGGGAACGTCTAGCAACC 250
102 CATC.....CACAGTGTGCCATCCACAGTGTGCCATCACTCCTGC. 143
          ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
251 CTTCTGTGGGGCTCAATTTTGGAATCTTGGAAGTACTTCAACTCCAGCA 300
144 .CCACAGCAGGAGCT..GGCTGGAGCATGAGGTGGATTCTGTG..CTGGA 188
          ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
301 ACTACATCTGCTCCTTCAAGTGGTTTGGGAACGGGCTCTTTGGATCTAA 350
```

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**FIG. 3B**

[illegible]



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## FIG. 3C

766 GGTGCAGGAGAACATCGCAGCCTTCGGGGGAGACCCAGGAAATGTGACCC 815  
|||||  
1050 GGTGCAGGAGAACATCGCAGCCTTCGGGGGAGACCCAGGAAATGTGACCC 1099  
816 TGTTTCGGCCAGTCGGCGGGGGGCCATGAGCATCTCAGGACTGATGATGTCA 865  
|||||  
1100 TGTTTCGGCCAGTCGGCGGGGGGCCATGAGCATCTCAGGACTGATGATGTCA 1149  
866 CCCCTAGCCTCGGGTCTCTTCCATCGGGCCATTTCCCAGAGTGGCACC GC 915  
|||||  
1150 CCCCTAGCCTCGGGTCTCTTCCATCGGGCCATTTCCCAGAGTGGCACC GC 1199  
916 GTTATTTCAGACTTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG 965  
|||||  
1200 GTTATTTCAGACTTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG 1249  
966 TTGCCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC 1015  
|||||  
1250 TTGCCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC 1299  
1016 TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCCAACAAGAT 1065  
|||||  
1300 TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCCAACAAGAT 1349  
1066 GAGATTCCTCCAACCTGAACCTCCAGAGAGACCCGGAAGAGATTATCTGGT 1115  
|||||  
1350 GAGATTCCTCCAACCTGAACCTCCAGAGAGACCCGGAAGAGATTATCTGGT 1399  
1116 CCATGAGCCCTGTGGTGGATGGTGTGGTGATCCCAGATGACCCCTTGGTG 1165  
|||||  
1400 CCATGAGCCCTGTGGTGGATGGTGTGGTGATCCCAGATGACCCCTTGGTG 1449  
1166 CTCCTGACCCAGGGGAAGGTTTCATCTGTGCCCTACCTTCTAGGTGTCAA 1215  
|||||  
1450 CTCCTGACCCAGGGGAAGGTTTCATCTGTGCCCTACCTTCTAGGTGTCAA 1499  
1216 CAACCTGGAATTCAATTGGCTCTTGCCTTATATCATGAAGTTCCCGCTAA 1265  
|||||  
1500 CAACCTGGAATTCAATTGGCTCTTGCCTTAT..... 1530  
.  
.  
.  
1316 CGCACCCCTGTTGAATATCACCAAGGAGCAGGTACCACTTGTGGTGGAGGA 1365  
|||||  
1531 .....AATATCACCAAGGAGCAGGTACCACTTGTGGTCGAGGA 1568  
1366 GTACCTGGACAATGTCAATGAGCATGACTGGAAGATGCTACGAAACCGTA 1415



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FIG. 3D

1416 TGATGGACATAGTTCAAGATGCCACTTTCGTGTATGCCCACTGCAGACT 1465  
|||||  
1619 TGATGGACATAGTTCAAGATGCCACTTTCGTGTATGCCCACTGCAGACT 1668  
  
1466 GCTCACTACCACCGAGATGCCGGCCTCCCTGTCTACCTGTATGAATTTGA 1515  
|||||  
1669 GCTCACTACCACCGA..... 1683  
  
.....  
  
1666 CAACTTTGCCCCGCACAGGAAACCCCAATGATGGGAATCTGCCCTGCTGGC 1715  
|||||  
1684 .....GAAACCCCAATGATGGGAATCTGCCCTGCTGGC 1716  
  
1716 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTTACCACAAGA 1765  
|||||  
1717 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTTACCACAAGA 1766  
  
1766 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTTTGGATGAGTCTGTA 1815  
|||||  
1767 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTTTGGATGAGTCTGTA 1816  
  
1816 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1865  
|||||  
1817 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1866  
  
1866 GGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGAC 1915  
|||||  
1867 GGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGAC 1916  
  
1916 TAGCCATGGACATACCTGGGGACAAGAGTTCTACCCAAGGGCGAATTCGT 1965  
|||||  
1917 TAGCCATGGACATACCTGGGGACAAGAGTTCTACCCA...CCCCA...GT 1960  
  
1966 TTAAACCTGCAGGA.CTAG..... 1983  
|||  
1961 TTAGAACTGCAGGAGCTCCCTGCTGCCTCCAGGCCAAAGCTAGAGCTTTT 2010  
  
.....





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FIG. 4C

460	470	480	490	500	510
COE-2	HRDAGLPVLYE	FEHARGIIVK	PRTDGADH	GDEMYFL	FGPPFATGL
	...	...	...	...	SMGKEKALS
pro873	HRET--PMM	---	GIC--P	---	AGHA-----
					520
520	530	540	550	560	570
COE-2	KYWANFARTGN	PNDGNLPCW	PRYNKDEKYL	QLDFTTRVGM	KLKEKKMAFW
			...	...	...
pro873	---	---	---	TTRM-----	KSTCSWIL-----P-
				530	540
580					
COE-2	KQRQF				
	..				
pro873	-QEWA				

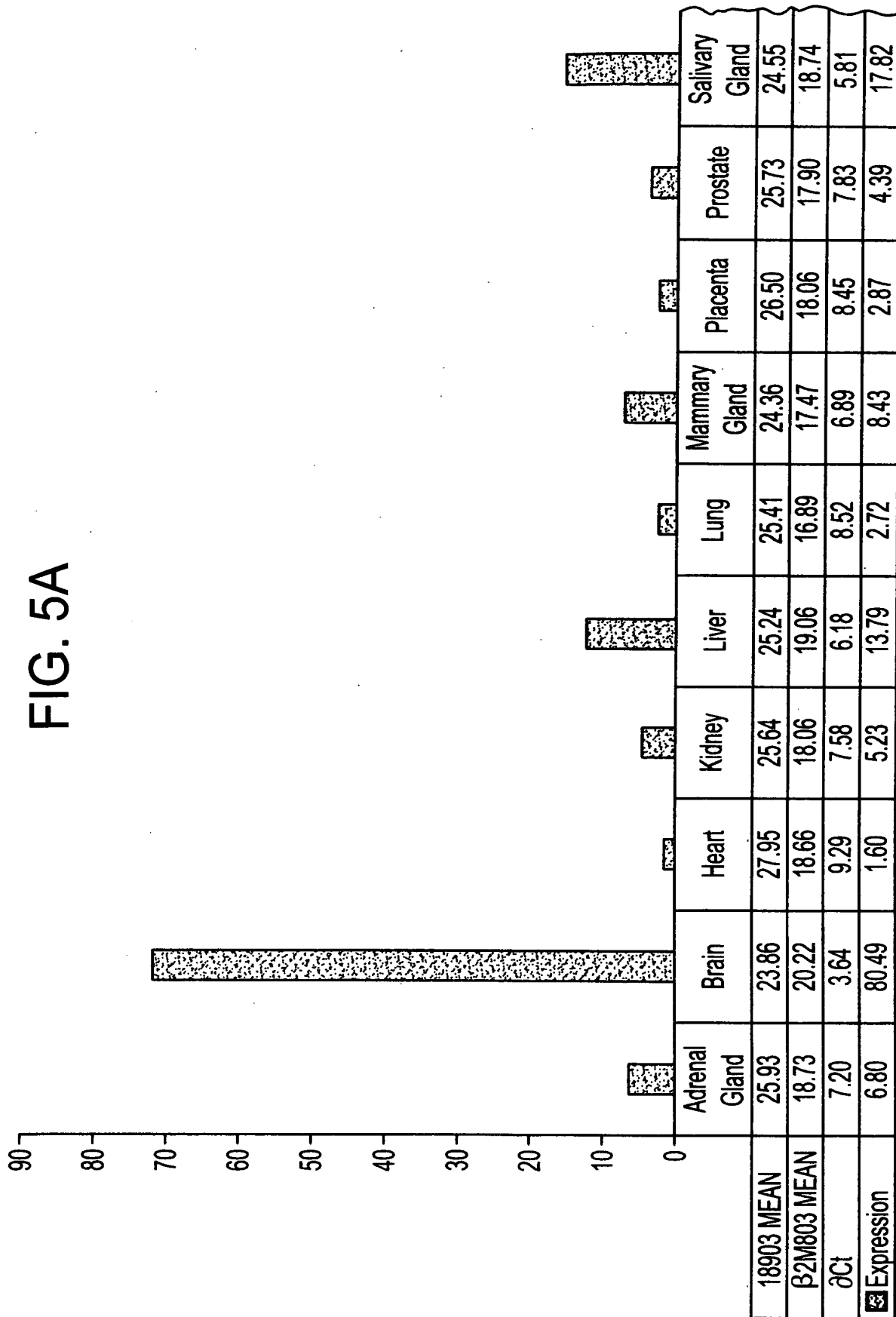


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FIG. 5A





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FIG. 5B

Muscle	Sm. Intestine	Spleen	Stomach	Teste	Thymus	Trachea	Uterus	Spinal Cord	Skin	DRG
29.70	25.43	26.89	26.27	24.29	26.33	25.14	26.18	23.99	23.01	25.06
20.66	17.86	16.37	18.03	19.32	18.19	19.10	18.53	19.20	17.10	19.07
9.04	7.58	10.52	8.25	4.97	8.15	6.04	7.66	4.80	5.91	5.99
1.91	5.24	0.68	3.30	31.91	3.53	15.25	4.96	36.02	16.63	15.73

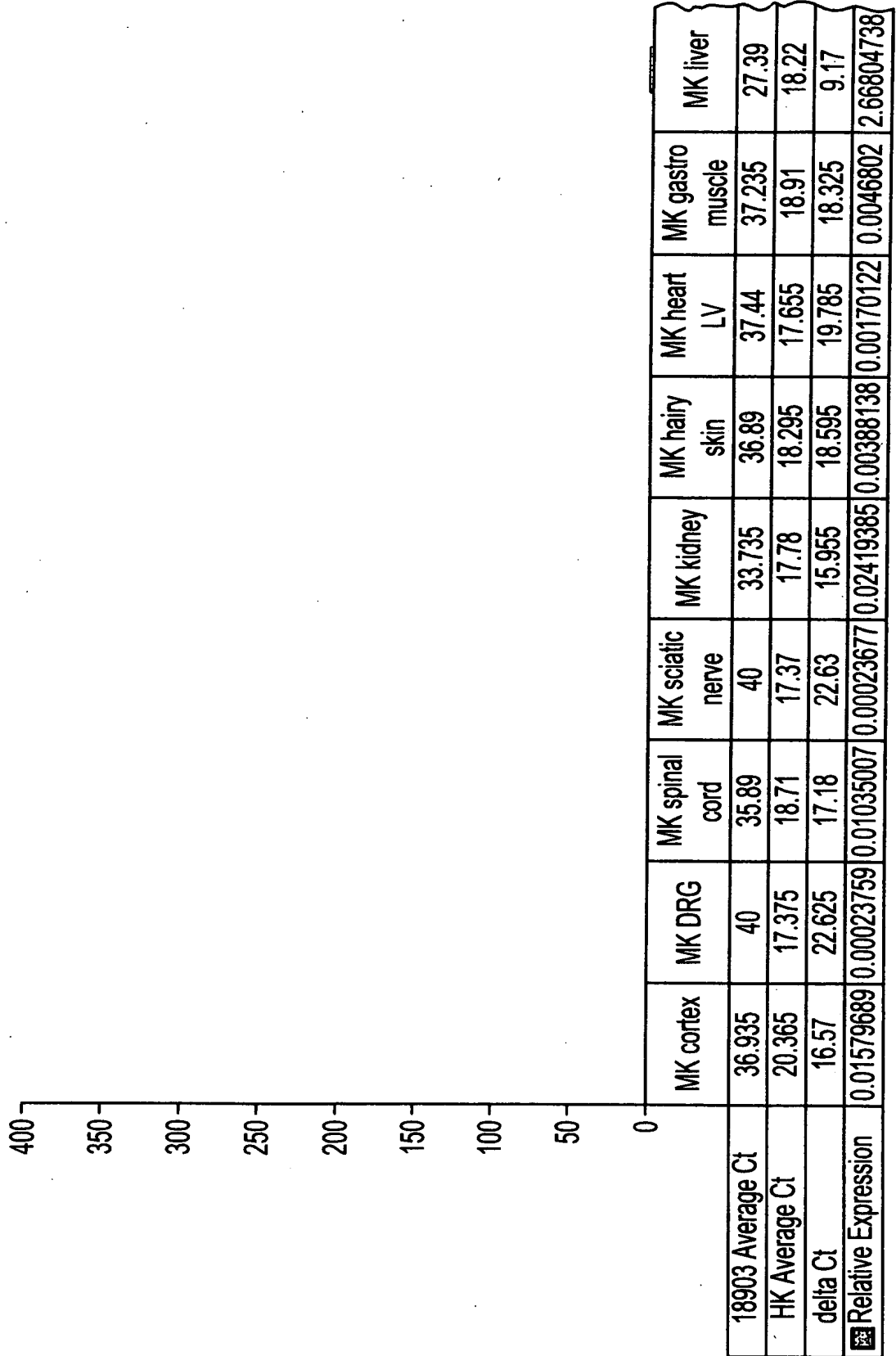


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## FIG. 6A





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FIG. 6B

				Hu. Brain	Hu. Spinal cord	Hu. Heart	Hu. Kidney
				Hu. Liver	Hu. Lung		
				21.27	23.78	28.26	26.155
				19.245	18.295	17.855	17.925
				2.025	5.485	10.405	8.23
				377.618146	34.3154004	1.13349992	5.11872423
				10.3803579	9.935	1.57002147	

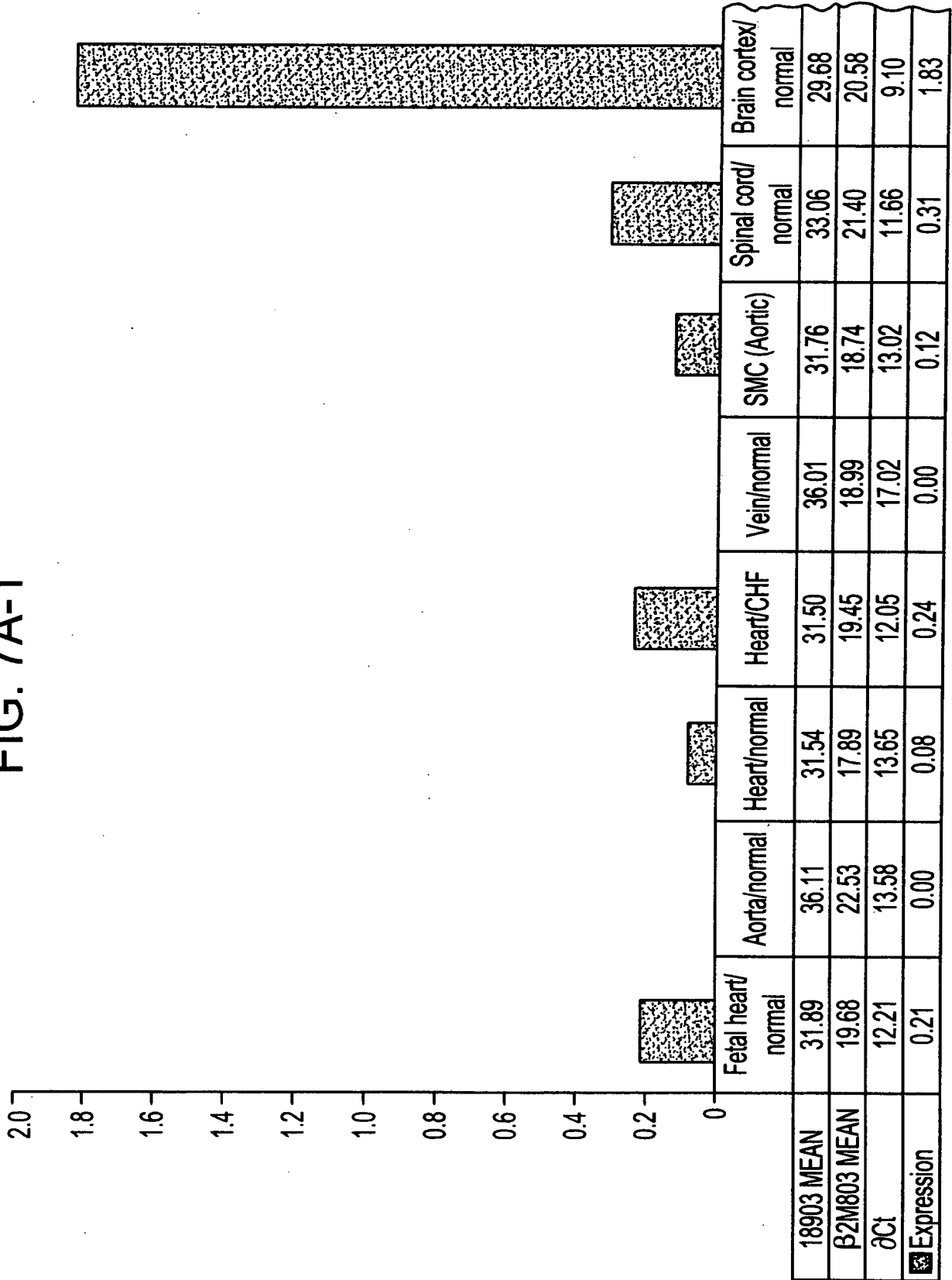


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FIG. 7A-1







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FIG. 7A-2

Brain hypothalamus	Glial cells (Astrocytes)	Brain/ Glioblastoma	Breast/ normal	Breast tumor/ IDC	OVARY/ Normal	OVARY/ Tumor	Pancreas	Prostate/ Normal	Prostate/ Tumor
29.45	33.94	30.39	30.10	30.75	31.73	33.59	30.88	31.16	29.03
19.24	21.09	17.43	18.60	17.66	19.95	18.91	17.33	18.34	17.57
10.21	12.86	12.97	11.50	13.09	11.79	14.68	13.55	12.83	11.46
0.85	0.13	0.13	0.35	0.11	0.28	0.04	0.08	0.14	0.35



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FIG. 7A-3

Condition	Colon/normal	Colon/tumor	Colon/IBD	Kidney/normal	Liver/normal	Liver fibrosis	Fetal Liver/normal	Lung/normal	Lung/tumor
Value 1	32.03	30.80	32.37	30.98	31.82	30.10	33.55	30.54	30.30
Value 2	17.78	18.15	17.72	20.03	19.08	18.82	21.39	17.31	17.77
Value 3	14.26	12.66	14.65	10.95	12.75	11.29	12.16	13.23	12.53
Value 4	0.05	0.16	0.04	0.51	0.15	0.40	0.22	0.10	0.17

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FIG. 7A-4

Lung/COPD	Tonsil/normal	Lymph node/normal	Thymus/normal	Epithelial Cells (Prostate)	Endothelial Cells (Aortic)	Skeletal Muscle	Fibroblasts (Dermal)	Skin/Normal	Adipose/Normal
29.44	31.13	31.40	32.80	30.70	35.27	31.06	33.10	31.16	32.43
17.10	17.19	17.91	20.03	20.13	20.16	18.26	18.18	20.29	17.96
12.34	13.94	13.49	12.78	10.57	15.11	12.81	14.92	10.87	14.47
0.19	0.06	0.09	0.14	0.66	0.03	0.14	0.03	0.54	0.04





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FIG. 7A-5

Osteoblasts (Primary)	Osteoblasts (Undiff)	Osteoblasts (Diff)	Osteoclasts	Aorta SMC (Early)	Aorta SMC (Late)	HUVEC	HMVEC
34.84	33.19	33.23	32.47	32.50	32.72	32.17	32.74
20.44	18.50	17.83	17.25	19.53	18.77	19.27	18.74
14.40	14.69	15.40	15.22	12.97	13.96	12.91	14.00
0.05	0.04	0.02	0.03	0.13	0.06	0.13	0.06



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## FIG. 7B

Tissue	18903 MEAN	$\beta$ 2M803 MEAN	$\delta$ Ct	Expression
Fetal heart/normal	31.89	19.68	12.21	0.21
Aorta/normal	36.11	22.53	13.58	0.00
Heart normal	31.54	17.89	13.65	0.08
Heart/CHF	31.50	19.45	12.05	0.24
Vein/normal	36.01	18.99	17.02	0.00
SMC (Aortic)	31.76	18.74	13.02	0.12
Spinal cord/normal	33.06	21.40	11.66	0.31
Brain cortex/normal	29.68	20.58	9.10	1.83
Brain hypothalamus/normal	29.45	19.24	10.21	0.85
Glial cells (Astrocytes)	33.94	21.09	12.86	0.13
Brain/Glioblastoma	30.39	17.43	12.97	0.13
Breast/normal	30.10	18.60	11.50	0.35
Breast tumor/IDC	30.75	17.66	13.09	0.11
Ovary/normal	31.73	19.95	11.79	0.28
Ovary/tumor	33.59	18.91	14.68	0.04
Pancreas	30.88	17.33	13.55	0.08
Prostate/normal	31.16	18.34	12.83	0.14
Prostate/tumor	29.03	17.57	11.46	0.35
Colon/normal	32.03	17.78	14.26	0.05
Colon/tumor	30.80	18.15	12.66	0.16
Colon/IBD	32.37	17.72	14.65	0.04
Kidney/normal	30.98	20.03	10.95	0.51
Liver/normal	31.82	19.08	12.75	0.15
Liver/fibrosis	30.10	18.82	11.29	0.40
Fetal Liver/normal	33.55	21.39	12.16	0.22
Lung/normal	30.54	17.31	13.23	0.10
Lung/tumor	30.30	17.77	12.53	0.17
Lung/COPD	29.44	17.10	12.34	0.19
Tonsil/normal	31.13	17.19	13.94	0.06
Lymph node/normal	31.40	17.91	13.49	0.09
Thymus/normal	32.80	20.03	12.78	0.14
Epithelial Cells(prostate)	30.70	20.13	10.57	0.66
Endothelial Cells(aortic)	35.27	20.16	15.11	0.03
Skeletal Muscle/normal	31.06	18.26	12.81	0.14
Fibroblasts (Dermal)	33.10	18.18	14.92	0.03
Skin/normal	31.16	20.29	10.87	0.54
Adipose/normal	32.43	17.96	14.47	0.04
Osteoblasts (primary)	34.84	20.44	14.40	0.05
Osteoblasts (Undiff)	33.19	18.50	14.69	0.04
Osteoblasts (Diff)	33.23	17.83	15.40	0.02
Osteoblasts	32.47	17.25	15.22	0.03
Aorta SMC (Early)	32.50	19.53	12.97	0.13
Aorta SMC (Late)	32.72	18.77	13.96	0.06
HUVEC	32.17	19.27	12.91	0.13
HMVEC	32.74	18.74	14.00	0.06
	40.00	40.00	0.00	